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MINNESOTA UNIV MINNEAPOLIS DEPT OF CHEMISTRY
SYNTHESIS OF ANTIMALARIALS BY A NEW ROUTE TO 4-QUINOLINOLS, 4-Q--ETC(U)
MAR 77 W E NOLAND

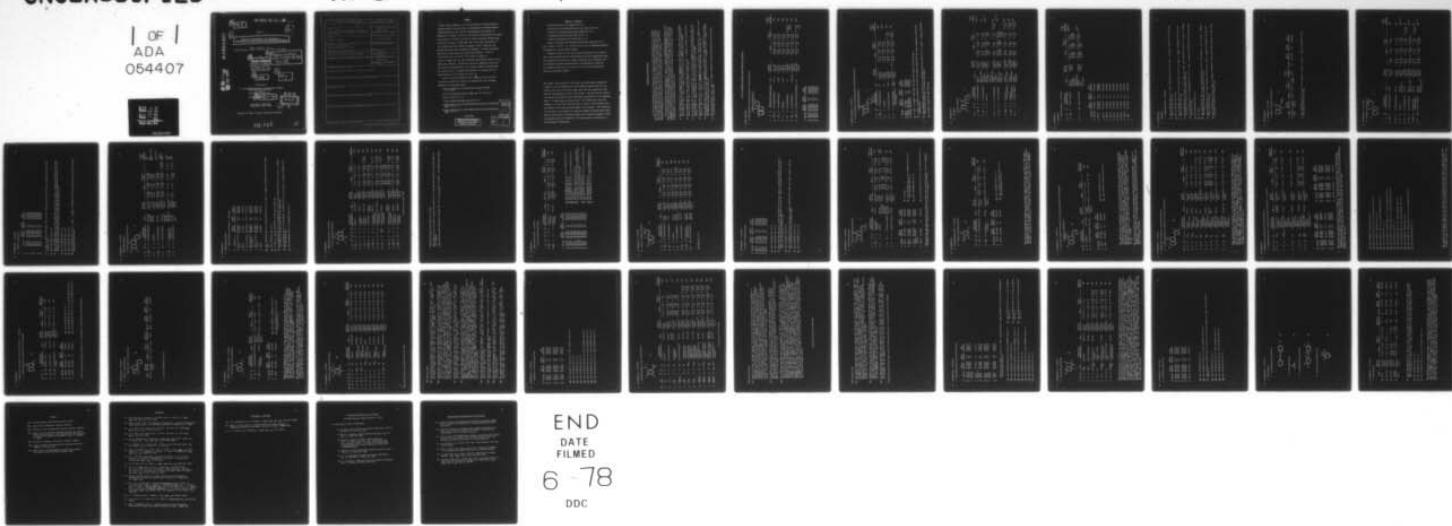
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Synthesis of Antimalarials by a New Route to
4-Quinolinols, 4-Quinazolinones, and 4-Cinnolinol 1-Oxides

Final Scientific Report
Contract Period: June 22, 1967-Dec. 31, 1969 (2 1/2 years)

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SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)		

Summary

Nine target compounds, six 4-(4-diethylamino-1-methylbutylamino)-3-phenylquinolines (1) and three 4-(4-diethylamino-1-methylbutylamino)-3-phenylquinazolines (2), and 100 intermediates were prepared and submitted for testing. All six of the quinoline antimalarials (1) showed some evidence of activity, and four of them, containing 4-methoxy (1a), 4-unsubstituted (1c), 4-bromo (1d), and 4-nitro (1e) substituents in the 3-phenyl group were classed as active in mice, though only the methoxy derivative (1a) was classed as active at a dosage (320 mg/kg) below that at which some toxic deaths were observed. Three of the compounds, 1a, 1c, and 1e, were classed as active in chicks at dosages (80, 320, and 320 mg/kg, respectively) where no toxic deaths were observed. Although all three were submitted, only one of the quinazoline antimalarials, the 6-chloro-2-phenyl derivative (2c), was tested in mice; it showed strong evidence of activity, but not quite sufficient to be classed as active.

None of the 100 intermediates were classed as active in mice, but the best evidence of activity was observed with the following compounds (in decreasing order):

4-chloroanthranilic acid hydrochloride (16c) 80 mg/kg
T-C 3.1 days

N-(3,4-dichlorobenzoyl)isatin (18c) 160 T-C 3.1 and 2.9

Compound 11a 640 T-C 3.9

2-(4-nitrophenyl)isatogen (3e) 640 T-C 3.5

sodium 6-chloro-2-(3,4-dichlorophenyl)quinazoline-4-carboxylate
(12h) 640 T-C 2.9

methyl 6-chloro-2-(3,4-dichlorophenyl)quinazoline-4-carboxylate
(12i) 640 T-C 2.5

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Summary - continued

6-chloroanthranilic acid (16g) 640 T-C 2.3

4,6-dichloro-3-(4-methoxyphenyl)quinoline (8f) 640 T-C 1.8

4-chloro-3-(4-methylphenyl)quinoline (8b) 640 T-C 1.4

1-cinnamylpyridinium chloride (19) 160 T-C 1.3

6-chloro-2-nitrobenzoic acid (22) 640 T-C 1.3

methyl 5-chloro-N-(4-nitrobenzoyl)anthranilate (17i) 640 T-C 1.1

More complete details are provided in the List of Compounds Prepared and Submitted for Testing which follows.

Financial support for the contract was discontinued by its sponsor after it was decided that the 4-aminoquinoline (1) and 4-aminoquinazoline (2) antimalarials would have to compare favorably with chloroquine, and the 2-phenyl-4-quinazoline aminoalcohols (the synthesis of which was not completed) would have to be free of or very low in phototoxicity, which was considered unlikely.

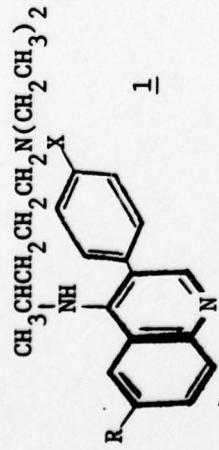
Note added: While approval of this report was being awaited, samples of a number of the new compounds for which elemental analyses had not been reported (and which are now over eight years old) were subjected to mass spectral analysis, without further purification. The mass spectral results are reported as footnotes to the tables where descriptions of the compounds appear. In some cases the results support the formulas and structures assigned. In other cases they show that, at least in their present state, the samples are not what had been thought or are mixtures. This underlines the fact that, in the absence of supporting elemental analyses and/or mass spectral verification of molecular weight, the structures assigned to those new compounds which are included in the tables should be viewed with a healthy degree of skepticism.

Antimalarial Test Results

For the tests designated with (infected) mice or chicks the date (day/month/year) of the computer printout is then given in parentheses, followed by the highest dosage given (subcutaneously), in mg./kg. of body weight, which did not cause toxic deaths. This is followed by the change in mean survival time in days, T-C (mean survival time of treated animals - mean survival time of controls), and then the corresponding data for higher dosages, if any, which caused toxic deaths as noted. Compounds are designated as active when an increase of 100% or more in mean survival time is observed.

With mosquito screening tests, designated as P. gall. A. aegypti, Plasmodium gallinaceum (Strain B) was used to infect a standard strain of Aedes aegypti. The date (day/month/year) of the computer printout is then given, followed by the concentration of the test compound, 0.1% unless toxic deaths were found to be predominant, in the 10% sucrose solution fed to the mosquitoes. This is followed by the % of toxic deaths observed relative to a control and then by any observations of abnormal oocysts or suppression of oocysts or sporozoites, or their absence, designated by neg.

- 1a mice (31/07/68) 320 T-C 6.1 active, 640 T-C 7.9 active but 3 toxic deaths at 4 days, 640 T-C 8.9 active but 2 toxic deaths at 4 days; chick (01/10/68, 19/11/68) 80 T-C 3.7 active, 160 T-C 5.0 active but 1 toxic death at 1 day; P. gall. A. aegypti (26/06/69) 0.1% 6% toxic deaths (control 9%) neg.
- 1b mice (14/04/69) 640 T-C 1.8 but 3 toxic deaths at 4 days; P. gall. A. aegypti (17/04/69) 0.01% 9% toxic deaths (control 9%) neg., 0.1% 100% toxic deaths (control 26%)
- 1c mice (31/07/68) 160 T-C 5.3 (01/10/68) 160 T-C 4.9, 320 T-C 8.2 active but 1 toxic death at 4 days, 640 T-C 9.7 active but 3 toxic deaths at 4 days; chick (31/07/68) 320 T-C 6.7 active (16/01/69) 480 T-C 5.5 active; P. gall. A. aegypti (26/09/69) 0.1% 63% toxic deaths (control 23%) neg.
- 1d mice (31/07/68) 320 T-C 5.1, 640 T-C 8.4 active but 3 toxic deaths at 4 days, 640 T-C 8.9 active but 3 toxic deaths at 4 days; P. gall. A. aegypti (26/06/69) 0.1% 74% toxic deaths (control 9%) neg.
- 1e mice (21/08/68) 160 T-C 4.3, 320 T-C 6.9 active but 1 toxic death at 4 days (01/10/68) 160 4.3, 320 T-C 8.9 active but 1 toxic death at 4 days; chick (31/07/68) 320 T-C 6.5 active; P. gall. A. aegypti (26/06/69) 0.1% 11% toxic deaths (control 9%) neg.
- 1f mice (14/04/69) 640 T-C 0.8; P. gall. A. aegypti (17/04/69) 0.01% 26% toxic deaths (control 9%) neg., 0.1% 100% toxic deaths (control 26%)

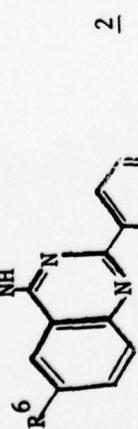
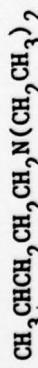
List of Compounds Prepared and Submitted for Testing**I. Target Compounds****A. 4-(4-Diethylamino-1-methylbutylamino)-3-phenylquinolines**

<u>1</u>	<u>X</u>	<u>R</u>	<u>Substituent Identification</u>	<u>mp°</u>	<u>Formula Mol. Wt.</u>	<u>Anal.</u>	<u>Calcd. % Found</u>	<u>Source and Reference</u>
								<u>Source and Reference</u>
<u>a</u>	OCH ₃	H	3-(4-methoxyphenyl)	67-70	C ₂₅ H ₃₃ N ₃ O 391.54	C 76.68 H 8.50 N 10.73 76.64 8.61 10.74	MAS	
<u>b</u>	CH ₃	H	3-(4-methylphenyl)	62-63	C ₂₅ H ₃₃ N ₃ 375.54	C 79.95 H 8.86 N 11.19 79.84 8.81 11.13	MAS	
<u>c</u>	H	H	3-phenyl	59-61	C ₂₄ H ₃₁ N ₃ 361.51	C 79.73 H 8.64 N 11.62 79.67 8.47 11.44	MAS	
<u>d</u>	Br	H	3-(4-bromophenyl)	70	C ₂₄ H ₃₀ N ₃ Br 440.42	C 65.45 H 6.87 N 9.54 Br 18.15 65.69 7.19 9.63 16.20	MAS	
<u>e</u>	NO ₂	H	3-(4-nitrophenyl)	brown oil	C ₂₄ H ₃₀ N ₃ O ₂ 406.51	C 70.91 H 7.44 N 13.78 70.82 7.68 13.61	MAS	
<u>f</u>	OCH ₃	C1	6-chloro-3-(4-methoxyphenyl)	oil	C ₂₅ H ₃₂ N ₃ OCl 425.99	C 70.48 H 7.57 N 9.87 C1 8.32 70.40 7.59 9.86 7.59	MAS	
								7.55

<u>1</u>	<u>Our No.</u>	<u>Walter Reed No.</u>	<u>Sample Size, g.</u>	<u>Date Received</u>
<u>a</u>	NS-29	AD 22742	2.5	01/05/68
<u>b</u>	NS-48	AF 52562	2.5	29/10/68
<u>c</u>	NS-6	AD 22706	2.5	01/05/68
<u>d</u>	NS-32	AD 22751	2.5	01/05/68
<u>e</u>	NS-28	AD 22733	2.5	01/05/68
<u>f</u>	NS-53	AF 52606	2.5	29/10/68

I. Target Compounds - continued

B. 4-(4-Diethylamino-1-methylbutylamino)-2-phenylquinazolines



<u>2</u>	<u>X</u>	<u>R⁶</u>	<u>Substituent Identification</u>	<u>mp°</u>	<u>Formula Mol. Wt.</u>	<u>Anal.</u>	<u>Calcd. % Found</u>	<u>Source and Reference</u>
<u>a</u>	<u>OCH₃</u>	<u>H</u>	<u>2-(4-methoxyphenyl)</u>	<u>oil</u>	<u>C₂₄H₃₂N₄O 392.53</u>	<u>C 73.43 H 8.22 N 14.27 72.35 8.33 14.00</u>	<u>MAS</u>	
<u>b</u>	<u>H</u>	<u>H</u>	<u>2-phenyl</u>	<u>oil</u>	<u>C₂₃H₃₀N₄ 362.50</u>	<u>C 76.20 H 8.34 N 15.46 76.36 8.47 15.19</u>	<u>MAS^a</u>	
<u>c</u>	<u>H</u>	<u>C1</u>	<u>6-chloro-2-phenyl</u>	<u>78-86</u>	<u>C₂₃H₂₉N₄C1 396.95</u>	<u>C 69.59 H 7.36 N 14.12 C1 8.93 69.71 7.70 14.08 8.78</u>	<u>KTK</u>	
<u>c'</u>	<u>H</u>	<u>C1</u>	<u>6-chloro-2-phenyl, sesquihydrochloride (= .1.5 HCl)</u>	<u>yellow solid</u>	<u>C₂₃H₂₉N₄C1 · 1.5 HCl C 451.65</u>	<u>H 6.81 N 12.41 C1 19.62 61.32 6.81 12.02 21.03</u>	<u>KTK</u>	

<u>2</u>	<u>Our No.</u>	<u>Walter Reed No.</u>	<u>Sample Size, g.</u>	<u>Date Received</u>
<u>a</u>	<u>NS-85</u>	<u>AU 24947</u>	<u>2.5</u>	<u>28/05/69</u>
<u>b</u>	<u>NS-80</u>	<u>AU 24929</u>	<u>2.0</u>	<u>28/05/69</u>
<u>c</u>	<u>JM-45-E</u>	<u>WR 93216-A?</u>	<u>1.85</u>	<u>14/12/67</u>
<u>c'</u>	<u>JM-20-G</u>	<u>WR 93216-B?</u>	<u>1.0</u>	<u>14/12/67</u>

2a P. gall. A. aegypti (05/11/69) 0.1% 90% toxic deaths (control 3%) neg.

2b P. gall. A. aegypti (05/11/69) 0.1% 40% toxic deaths (control 0%) 25% oocyst suppression (control 0%) otherwise neg.

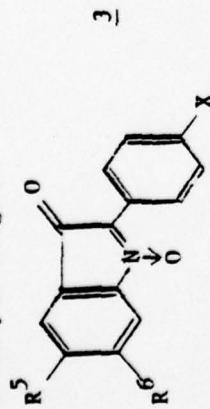
2c mice (04/04/68, Group 613) 640 T-C 4.0 (04/04/68, Group 615) 640 T-C 3.1; P. gall. A. aegypti (15/05/68) 0.01% 0% toxic deaths neg., 0.1% 100% toxic deaths

2c' no report (unless included under 2c)

II. Intermediates

A. Isatogens

1. 2-Phenylisatogens



<u>3</u>	<u>X</u>	<u>R</u> ⁵	<u>R</u> ⁶	Substituent Identification	mp°	Formula Mol. Wt.	Calcd. % Found	Anal.	Source and Reference
<u>a</u>	CH ₃ O	H	H	2-(4-methoxyphenyl)	187-188 193	C ₁₅ H ₁₁ NO ₃ 253.25	C 71.14 ^b 70.93 ^b	H 4.37 ^b 4.46 ^b	N 5.53 ^b 5.81 ^b
<u>b</u>	CH ₃	H	H	2-(4-methylphenyl)	208-209 237.25	C ₁₅ H ₁₁ NO ₂ C ₁₄ H ₉ NO ₂	C 75.93 75.32	H 4.67 4.06 ^c	N 5.90 5.94
<u>c</u>	H	H	H	2-phenyl	188-189 189.5-190.5 ^d 189-190 ^d	C ₁₄ H ₉ NO ₂ 223.22	C 75.46 ^d 75.52 ^d	H 4.25 ^d 4.34 ^d	N 6.28 ^d 6.25 ^d
<u>d</u>	Br	H	H	2-(4-bromophenyl)	186-187 orange-red	C ₁₄ H ₈ NO ₂ Br 302.13	C 55.65 55.37	H 2.67 2.78	N 4.64 4.57
<u>e</u>	NO ₂	H	H	2-(4-nitrophenyl)	261-262 250-254 dec ea orange-red	C ₁₄ H ₈ N ₂ O ₄ 268.22	C 62.69 62.61ea 62.90ea	H 3.01 ^{e,a} 3.08ea 3.01ea	N 10.45 ^{e,a} 10.50ea 10.59ea
<u>f</u>	CH ₃ O	Cl	H	5-chloro-2-(4-methoxyphenyl)	235-236 brown needles	C ₁₅ H ₁₀ NO ₃ Cl 287.70	C 62.62 62.38	H 3.50 3.41	N 4.87 4.83
<u>g</u>	CH ₃	Cl	H	5-chloro-2-(4-methylphenyl)	180-180.5 orange plates	C ₁₅ H ₁₀ NO ₂ Cl 271.70	C 66.31 66.03	H 3.71 3.66	N 5.15 5.07
<u>h</u>	H	Cl	H	5-chloro-2-phenyl	182-183 orange-red	C ₁₄ H ₈ NO ₂ Cl 257.67	C 65.25 65.07	H 3.13 3.22	N 5.44 5.45

II. Intermediates

A. Isatogens

1. 2-Phenylisatogens - continued

<u>3</u>	<u>X</u>	<u>R</u> ⁵	<u>R</u> ⁶	Substituent	<u>mp</u> °	Formula Mol. Wt.	Anal.	Calcd. % Found	Source and Reference
<u>1</u>	H	NO ₂	H	5-nitro-2-phenyl	240-241 234-235 240-243ga 238-239gb	C ₁₄ H ₈ N ₂ O ₄ 268.22	C 62.69 61.39 62.63ga 62.81gb	H 3.01 2.88 3.16ga 3.31gb	N 10.45 10.33 10.59ga 10.31gb
<u>1</u>	H	H	NO ₂	6-nitro-2-phenyl	210-211 206ha red plates	C ₁₄ H ₈ N ₂ O ₄ 268.22	C 62.69 63.39ha 62.70ha	H 3.01 3.35ha 3.46ha	N 10.45 10.34 JOB ^{f,a,h}

<u>3</u>	<u>Our No.</u>	Walter Reed No.	Sample Size, g.	Date Received
<u>a</u>	TRA-84-1	AC 66178	0.5	04/03/68
<u>b</u>	NS-45	AF 52535 AU 66267	0.5 0.3	29/10/68 23/06/69
<u>c</u>	MAS-3	AC 66123	0.5	04/03/68
<u>d</u>	MAS-19	AC 66150	0.5	04/03/68
<u>e</u>	MAS-9	AC 66132	0.5	04/03/68
<u>f</u>	NS-50	AF 52571	0.5	29/10/68
<u>g</u>	NS-89	AV 58091	0.3	01/12/69
<u>h</u>	MAS-15	AC 66141	0.5	04/03/68
<u>i</u>	MAS-26	AC 66169	0.5	04/03/68
<u>j</u>	JB8J	AC 66114	0.5	04/03/68

II. Intermediates

A. Isatogens

1. 2-Phenylisatogens - continued

3a mice (06/12/68) 640 T-C 0.5; chick (02/10/71) 320 T-C 0; P. gall. A. aegypti (10/10/68) 0.1% 23% toxic deaths (control 17%) neg.

3b mice (14/04/69) 640 T-C 0.8

3c mice (06/12/68) 640 T-C 0.5; chick (02/10/71) 320 T-C 0; P. gall. A. aegypti (10/10/68) 0.1% 17% toxic deaths (control 17%) neg.

3d mice (06/12/68) 640 T-C 0.9 but 3 toxic deaths at 4 days; chick (02/10/71) 320 T-C 0; P. gall. A. aegypti (10/10/68) 0.1% 9% toxic deaths (control 17%) neg.

3e mice (01/07/68) 640 T-C 3.5 (06/12/68) 640 T-C 3.9; P. gall. A. aegypti (10/10/68) 0.1% 26% toxic deaths (control 17%) neg.

3f mice (14/04/69) 640 T-C 1.2

3g no report

3h mice (06/12/68) 640 T-C 0.7; chick (02/10/71) 320 T-C 0 but 1 toxic death at 1 day; P. gall. A. aegypti (10/10/68) 0.1% 14% toxic deaths (control 17%) neg.

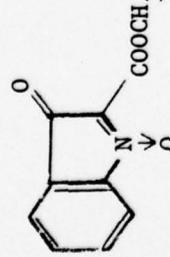
3i mice (06/12/68) 640 T-C 0.3; chick (02/10/71) 320 T-C 0; P. gall. A. aegypti (10/10/68) 0.1% 26% toxic deaths (control 17%) neg.

3j mice (31/07/68) 640 T-C 0.3; P. gall. A. aegypti (10/10/68) 0.1% 9% toxic deaths (control 3%) 75% oocyst suppression (control 25%) otherwise neg.

II. Intermediates

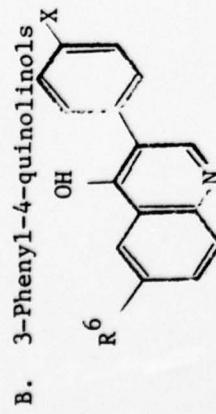
A. Isatogens - continued

2. Methyl Isatogen-2-carboxylate



<u>4</u>	<u>mp°</u>	<u>Formula</u>	<u>Calcd.</u> %		<u>Reference</u>	<u>Our No.</u>	<u>Walter Reed No.</u>	<u>Sample Size, g.</u>	<u>Date Received</u>
	<u>Mol. Wt.</u>	<u>Anal.</u>	<u>Found</u>	<u>Reed</u>		<u>A-1</u>			
a 201-202	C ₁₀ H ₇ NO ₄	C 58.54	H 3.44	N 6.83	SYA hb	A-1	AD 22671	0.5	01/05/68
201 hb	205.16	-	-	7.09	hb				

4 mice (31/07/68) 640 T-C 0.9 but 2 toxic deaths at 4 days; P. gall. A. aegypti (26/06/69) 0.1% 6% toxic deaths (23% control) neg.



<u>5</u>	<u>X</u>	<u>R</u> ⁶	Substituent Identification	<u>mp°</u>	Formula Mol. Wt.	Anal.	Calcd. % Found	Source and Reference
<u>a</u>	OCH ₃	H	3-(4-methoxyphenyl)	295-297	C ₁₆ H ₁₃ NO ₂ 251.27	C 76.47 76.48	H 5.22 5.16	N 5.57 5.33
<u>b</u>	CH ₃	H	3-(4-methylphenyl)	284-285	C ₁₆ H ₁₃ NO 253.27	C 81.68 81.38	H 5.57 5.39	N 5.95 5.70
<u>c</u>	H	H	3-phenyl	258-260 261.5-262	C ₁₅ H ₁₁ NO 221.25	C 81.43 81.56	H 5.01 5.08	N 6.33 6.18
<u>d</u>	Br	H	3-(4-bromophenyl)	312-314	C ₁₅ H ₁₀ NOBr 300.15	C 60.02 60.14	H 3.36 3.49	N 4.66 4.49
<u>e</u>	NO ₂	H	3-(4-nitrophenyl)	363-364 368-369	C ₁₅ H ₁₀ N ₂ O ₃ 266.25	C 67.66 67.50	H 3.79 3.95	N 10.52 10.27
<u>f</u>	OCH ₃	C1	6-chloro-3-(4-methoxyphenyl)	359-360	C ₁₆ H ₁₂ NO ₂ C1 285.72	C 67.25 67.37	H 4.24 4.16	N 4.90 4.64
<u>g</u>	H	NO ₂	6-nitro-3-phenyl	351-352 350-352	C ₁₅ H ₁₀ N ₂ O ₃ 266.25	C 67.66 67.94	H 3.79 4.07	N 10.52 10.85
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II. Intermediates - continued

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B. 3-Phenyl-4-quinolinols

<u>5</u>	<u>Our No.</u>	<u>Reed No.</u>	<u>Walter Reed No.</u>	<u>Sample Size, g.</u>	<u>Date Received</u>
<u>a</u>	NS-26	AD	55965	0.5	17/05/68
	NS-26A	AE	06789	0.25	11/06/68
<u>b</u>	NS-46	AF	52544	0.5	29/10/68
<u>c</u>	NS-4	AD	22680	0.5	01/05/68
<u>d</u>	NS-30	AD	55983	0.5	17/05/68
<u>e</u>	NS-44	AF	11427	0.5	24/09/68
<u>f</u>	NS-10	AD	22715	0.5	01/05/68
<u>g</u>	NS-51	AF	52580	0.5	29/10/68
	NS-33	AD	22760	0.5	01/05/68

5a P. gall. A. aegypti (06/11/68) 0.1% 11% toxic deaths (control 6%) 100% oocyst suppression (control 0%) otherwise neg.

5b mice (14/04/69) 640 T-C 0.2

5c mice (31/07/68) 160 T-C 0.7; chick (31/07/68) 320 T-C 0.1; P. gall. A. aegypti (10/10/68) 0.1% 17% toxic deaths (control 3%) 25% oocyst suppression (control 0%) 50% sporozoite suppression (control 0%), 0.1% no toxic deaths (control 6%) neg. (thus, not confirming the previous run)

5d mice (21/08/68) 640 T-C 0.7

5e mice (31/07/68) 640 T-C 0.1

5f mice (14/04/69) 640 T-C 0.2

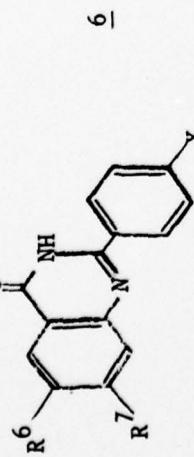
5g mice (31/07/68) 640 T-C 0.8; P. gall. A. aegypti (26/06/69) 0.1% 17% toxic deaths (control 9%) 25% oocyst suppression (control 0%)

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II. Intermediates - continued

C. $4(\underline{3H})$ -Quinazolinones

1. 2-Phenyl-4($\underline{3H}$)-quinazolinones



<u>6</u>	<u>X</u>	<u>R</u> ⁶	<u>R</u> ⁷	Substituent Identification	mp°	Formula Mol. Wt.		Anal.	Calcd. % Found	Source and Reference
						C ₁₅ H ₁₂ N ₂ O ₂	71.41kb			
<u>a</u>	OCH ₃	H	H	2-(4-methoxyphenyl)	246-248kb 257-259	C ₁₅ H ₁₂ N ₂ O ₂	71.41kb	H 4.80kb 5.04	N 11.11kb 11.29	JBH ¹
<u>b</u>	H	H	H	2-phenyl	250-251 240-241	C ₁₄ H ₁₀ N ₂ O	71.65 71.18	H 4.75 4.54	N 10.89 12.61	MAS ¹ MAS ^a ,lb,lc,ld
<u>c</u>	NO ₂	H	H	2-(4-nitrophenyl)	363-365	C ₁₄ H ₉ N ₃ O ₃	62.92kb	H 3.39	N 15.73kb	JBH ^{1a,1c,m}
<u>d</u>	H	C1	H	6-chloro-2-phenyl	298-300 298 dec 295-297	C ₁₄ H ₉ N ₂ OCl	65.51ka	H 3.53	N 15.99kb	JBH ^{1d,n} KT ^{1d,n}
<u>e</u>	NO ₂	C1	H	6-chloro-2-(4-nitrophenyl)	317-320 dec 285-300	C ₁₄ H ₈ N ₃ O ₃ C1	55.74	H 2.67 -	N 13.93 -	JBH ^{kb} KT ^K
<u>f</u>	H	H	C1	7-chloro-2-phenyl	271-281 292 ⁿ	C ₁₄ H ₉ N ₂ OCl	65.51	H 3.53 -	N 10.92 10.60 ⁿ	KT ⁿ C1 13.81 -

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II. Intermediates

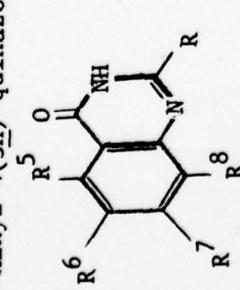
C. 4(3H)-Quinazolinones1. 2-Phenyl-4(3H)-quinazolinones - continued

<u>6</u>	<u>Our No.</u>	<u>Reed No.</u>	<u>Walter Reed No.</u>	<u>Sample Size, g.</u>	<u>Date Received</u>
<u>a</u>	JH I-13-14 gift NS-78	WR-93221-A AU 24901		0.45 0.5	14/12/67 28/05/69
<u>b</u>	NS-66	AU 24894		0.5	28/05/69
<u>c</u>	JH I-17-16 gift	WR-93220-A		0.62	14/12/67
<u>d</u>	JH I-41-30 gift JM-4 (JH-JH)	WR-93219-A AW 98545		0.5 0.6	14/12/67 16/04/70
<u>e</u>	JH I-57-2 gift JM-55	WR-93218-A AW 49462		0.5 0.4	14/12/67 16/04/70
<u>f</u>	JM-114	AW 49480		0.6	16/04/70
<u>6a</u>	mice (04/04/68)	640 T-C 0 (05/11/69)	160 T-C 0.2; P. gall. A. aegypti	(15/05/68)	0.1% 14% toxic deaths neg.
<u>6b</u>	mice (05/11/69)	160 T-C 0.6			
<u>6c</u>	P. gall. A. aegypti (15/05/68)		0.1% 17% toxic deaths neg.		
<u>6d</u>	mice (04/04/68) (15/05/68)	640 T-C 0.2 (23/09/70) 0.1% 3% toxic deaths	640 T-C 0.7; chick (10/02/71) 25% oocyst suppression		
<u>6e</u>	mice (04/04/68)	640 T-C 0.6 (07/08/70), 6% toxic deaths neg.	23/09/70) 640 T-C 0.1; P. gall. A. aegypti (15/05/68)	0.1%	
<u>6f</u>	mice (04/04/68)	640 T-C 0 (07/08/70)	640 T-C 0.5		

II. Intermediates

C. 4(3H)-Quinazolinones - continued

2. 2-Alky1-4(3H)-quinazolinones



I	R	R⁵	R⁶	R⁷	R⁸	Substituent Identification	mp°	Formula	Mol. Wt.	Anal.	Calcd. % Found	Reference
a	CH₃	H	H	H	H	2-methyl	245.5-246.5	C₉H₈N₂O	160.17	C 67.48 H 5.03 N 17.49	-	KTK
b	CF₃	H	H	H	H	2-trifluoro- methyl*	218-221	C₉H₅N₂OF₃	214.15	C 50.48 H 2.35 N 13.08	-	KTK
c	CCl₃	H	H	H	H	2-trichloro- methyl	219.5-221	C₉H₅N₂OC₂Cl₃	263.52	C 41.02 H 1.91 N 10.63	C1 40.37	KTK
d		H	H	H	H	2-cyclohexyl	230-231	C₁₄H₁₆N₂O	73.65	N 10.39	40.29	KTK ^o
e		H	H	H	H	2-cyclohexyl, hydrochloride	226-227	C_{228.28} C₁₄H₁₇N₂OC₂Cl	73.91 ^o 227.91 ^o	H 7.06 N 7.16 ^o	N 12.27 ^o 12.36 ^o	KTK ^o
f	CCl₃	H	C1	H	H	6-chloro-2-tri- chloromethyl	262.5-264.5	C₉H₄N₂OC₂Cl₄	264.75	C 36.28 H 1.35 N 9.40	C1 47.60	KTK
g	CCl₃	H	H	NO₂	H	7-nitro-2-tri- chloromethyl†	243-246	C₉H₄N₂OC₂Cl₃	297.97	C 36.36 H 1.63 N 13.62	C1 47.72	KTK
h	CCl₃	H	H	C1	H	7-chloro-2-tri- chloromethyl	238-242	C₁₄H₁₅N₂OC₂Cl₄	308.52	C 35.03 H 1.31 N 13.84	C1 34.48	KTK
i		H	C1	H	H	5-chloro-2- cyclohexyl†	188-194	C₁₄H₁₅N₂OC₂Cl₄	262.73	C 35.48 H 1.50 N 13.84	-	KTK
j		H	C1	H	H	6-chloro-2- cyclohexyl	285-286.5	C₁₄H₁₅N₂OC₂Cl₄	262.73	C 64.00 H 5.75 N 10.66	C1 13.50	KTK

(footnotes are on next page)

*Molecular formula and structure are in doubt.

#The position of the nitro group is given incorrectly as 6- in the name and structure on the data sheet for this compound.

†High resolution mass spectrum m/e 262.0916 (M^+ , calcd for $C_{14}H_{15}N_2OCl$, 262.0873). The sample may be impure.

C. 4(3H)-Quinazolinones - continued

2. 2-Alkyl-4(3H)-quinazolinones

<u>I</u>	<u>R</u>	<u>R</u> ⁵	<u>R</u> ⁶	<u>R</u> ⁷	<u>R</u> ⁸	<u>Substituent</u>	<u>Identificiation</u>	<u>mp°</u>	<u>Mol. Wt.</u>	<u>Anal.</u>	<u>Calcd. % Found</u>	<u>Source or Reference</u>
<u>k</u>	<u>S</u>	H	H	C1	H	7-chloro-2-cyclohexyl		255.5-256	<u>C₁₄H₁₅N₂OCl</u>	C 64.00 H 5.75 N 10.66 C1 13.50	KTK	
<u>l</u>	<u>S</u>	H	H	H	C1	8-chloro-2-cyclohexyl		241-244	<u>C₁₄H₁₅N₂OCl</u>	C 64.00 H 5.75 N 10.66 C1 13.50	KTK	

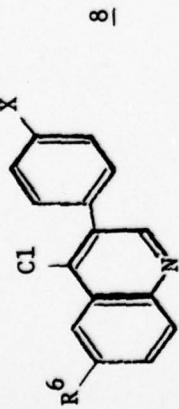
<u>I</u>	<u>Our No.</u>	<u>Walter Reed No.</u>	<u>Sample Size, g.</u>	<u>Date Received</u>
a	JM-127	AW 49382	0.5	16/04/70
b	JM-141	AW 49426	0.6	16/04/70
c	JM-131	AW 49417	0.6	16/04/70
d	JM-85	AW 49391	0.6	16/04/70
e	JM-70	AW 49408	0.1	16/04/70
f	JM-135	AW 49453	0.15	16/04/70
g	JM-138	AW 49515	0.6	16/04/70
h	JM-136	AW 49499	0.6	16/04/70
i	JM-110	AW 49435	0.15	16/04/70
j	JM-64	AW 49444	0.6	16/04/70
k	JM-80	AW 49471	0.6	16/04/70
l	JM-97	AW 49506	0.6	16/04/70

<u>7a</u>	mice (07/08/70)	640 T-C 0.3; chick (07/08/70) 120 T-C 0
<u>7b</u>	mice (07/08/70)	640 T-C 0.7
<u>7c</u>	mice (07/08/70)	640 T-C 0.5
<u>7d</u>	mice (07/08/70)	640 T-C 0.1; chick (07/08/70) 160 T-C 0
<u>7e</u>	no report	
<u>7f</u>	mice (07/08/70, 23/09/70)	160 T-C 0.7
<u>7g</u>	mice (07/08/70)	160 T-C 0.3, 320 T-C 0.9, 3 toxic deaths at 4 days, 640 5 toxic deaths at 4 days (incorrectly listed on printout as the 7-nitro derivative)
<u>7h</u>	mice (07/08/70)	640 T-C 0.1
<u>7i</u>	mice (07/08/70, 23/09/70)	160 T-C 0.1; chick (07/08/70) 100 T-C 0
<u>7j</u>	mice (07/08/70)	640 T-C 0.1
<u>7k</u>	mice (07/08/70)	640 T-C 0.3; chick (07/08/70) 160 T-C 0
<u>7l</u>	mice (07/08/70)	640 T-C 0.1; chick (07/08/70) 100 T-C 0

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II. Intermediates - continued

D. 4-Chloro-3-phenylquinolines



<u>8</u>	<u>X</u>	<u>R</u> ⁶	Substituent Identification	<u>mp</u> [°]	Formula Mol. Wt.	Anal.	Calcd. % Found	Source or Reference	
<u>a</u>	OCH ₃	H	3-(4-methoxyphenyl)	92-93 95-96	C ₁₆ H ₁₂ NOC ₁ 269.72	C 71.24 71.21	N 5.19 4.40	C1 13.15 12.96	
<u>b</u>	CH ₃	H	3-(4-methylphenyl)	71-72	C ₁₆ H ₁₂ NC ₁ 253.72	C 75.74 76.03	N 5.52 4.72	C1 13.97 13.91	
<u>c</u>	H	H	3-phenyl	72-73 74-75P	C ₁₅ H ₁₀ NC ₁ 239.70	C 75.16 75.4 P	H 4.21 4.4 P	N 5.84 -	
<u>d</u>	Br	H	3-(4-bromophenyl)	119-121 120-120.5	C ₁₅ H ₉ NBrC ₁ 318.60	C 56.54 56.76	H 2.85 2.88	N 4.40 4.18	C1 22.26* 21.85*
<u>e</u>	NO ₂	H	3-(4-nitrophenyl)	194-196	C ₁₅ H ₉ N ₂ O ₂ C ₁ 284.70	C 63.28 63.62	H 3.19 3.26	N 9.84 9.75	C1 12.45 12.45
<u>f</u>	OCH ₃	Cl	6-chloro-3-(4-methoxyphenyl)	158-159 156-167	C ₁₆ H ₁₁ NOC ₁ ₂ 304.17	C 63.18 63.22	H 3.65 3.68	N 4.60 4.48	C1 23.31 23.14
<u>g</u>	H	N ₂	6-nitro-3-phenyl	162-163 167-168	C ₁₅ H ₉ N ₂ O ₂ C ₁ 284.70	C 63.28 64.24	H 3.19 3.59	N 9.84 9.40	C1 12.45 11.98

*Includes Br as Cl.

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II. Intermediates - continued

D. 4-Chloro-3-phenylquinolines

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<u>8</u>	<u>Our No.</u>	<u>Walter Reed No.</u>	<u>Sample Size, g.</u>	<u>Date Received</u>
<u>a</u>	NS-27	AD 55974	0.5	17/05/68
<u>b</u>	NS-47	AF 52553	0.5	29/10/68
<u>c</u>	NS-5	AD 22699	0.5	01/05/68
<u>d</u>	NS-31	AD 55992	0.5	17/05/68
<u>e</u>	NS-11	AD 22724	0.5	01/05/68
<u>f</u>	NS-52	AF 52599	0.5	29/10/68
<u>g</u>	NS-34	AD 56006	0.5	17/05/68

8a mice (21/08/68) 640 T-C 0.38b mice (14/04/69) 640 T-C 1.4

8c mice (31/07/68) 160 T-C 0.7; chick (31/07/68) 320 T-C 0.1; P. gall. A. aegypti (10/10/68) 0.1% 9% toxic deaths (control 3%) 25% sporozoite suppression (control 0%), 0.1% 3% toxic deaths (control 6%) neg.
 (thus, not confirming the previous run)

8d mice (21/08/68) 640 T-C 0.1

8e mice (31/07/68) 640 T-C 0.3; P. gall. A. aegypti (26/06/69) 0.1% 100% toxic deaths (control 23%) 50% oocyst suppression (control 0%) otherwise neg.

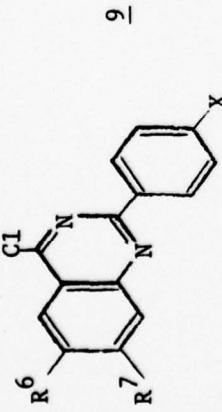
8f mice (14/04/69) 640 T-C 1.88g mice (21/08/68) 640 T-C 0.1

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II. Intermediates - continued

E. 4-Chloroquinazolines

1. 4-Chloro-2-phenylquinazolines



9	X	R ⁶	R ⁷	Substituent	Identificat ^o n	mp ^o	Formula	Anal.	Calcd. %	Found	Source or Reference
							Mol. Wt.				
a	OCH ₃	H	H	2-(4-methoxy-phenyl)		121-122	C ₁₅ H ₁₁ N ₂ OCl	C 66.55 H 4.09 N 10.35	C1 13.10 10.10	12.92	MAS
b	H	H	H	2-phenyl		128-129	C ₁₄ H ₉ N ₂ Cl	C 69.86 H 3.77 N 11.64	C1 14.73 11.84	-	MAS a, q KTK
c	H	Cl	H	6-chloro-2-phenyl		127.5-128.5 124-124.5 ^a 127-128 ^q	C ₁₄ H ₈ N ₂ Cl ₂	C 71.13 4.16 3.95 ^a 3.74 ^q	- - - 11.34 ^q	- - - 14.88 ^a	-
d	H	H	C1	7-chloro-2-phenyl		159.5-160 157-159	C ₁₄ H ₈ N ₂ Cl ₂ *	C 61.11 H 2.93 61.12 2.92	C1 25.78 10.18 10.16	25.38	KTK
						240-265	C ₁₄ H ₈ N ₂ Cl ₂ *	C 61.11 H 2.93	C1 25.78	KTK	
						275.13	-	-	-	-	

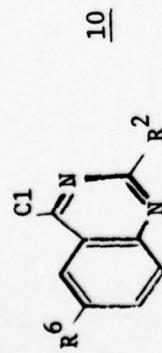
9	Our No.	Walter Reed No.	Sample Size, g.	Date Received
a	NS-84	AU 24938	0.5	28/05/69
b	NS-79	AU 24910	0.5	28/05/69
	JM-24	AW 49551	0.5	16/04/70
c	JM-4-A	WR-93217-A	0.504	14/12/67
	JM-11E	AW 49917 (JM-11)	0.35	23/04/70
d	JM-121	AW 49588	0.6	16/04/70

*High resolution mass spectrum m/e (rel intensity) 274.0057 (36), 274.0038 (39)^(M⁺), calcd for C₁₄H₈N₂Cl₂, 274.0065); 239.0425 (100), 239.0370 (100) [(M - Cl)⁺, calcd for C₁₄H₈N₂Cl, 239.0377].

II. Intermediates

E. 4-Chloroquinazolines - continued

2. 2-Alkyl-4-chloroquinazolines



<u>10</u>	<u>R<sup>2</sup></u>	<u>R<sup>6</sup></u>	<u>Substituent</u>	<u>mp°</u>	<u>Formula</u>	<u>Anal.</u>	<u>Calcd. % Found</u>	<u>Source or Reference</u>	
					<u>Mol. Wt.</u>				
<u>a</u>	CCl ₃	H	2-trichloromethyl	127-128.5	C ₉ H ₄ N ₂ Cl ₄ 281.97	C 38.33 38.14	H 1.43 1.40	N 9.94 9.77	C1 50.30 50.54
<u>b</u>		C1	6-chloro-2-cyclohexyl*	108-128	C ₁₄ H ₁₄ N ₂ Cl ₂ *C 281.18	-	H 5.02	N 9.96	C1 25.22

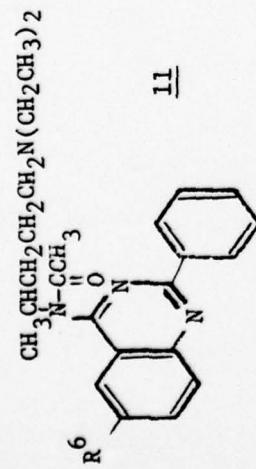
<u>10</u>	<u>Our No.</u>	<u>Walter Reed No.</u>	<u>Sample Size, g.</u>	<u>Date Received</u>
<u>a</u>	JM-132	AW 49560	0.6	16/04/70
<u>b</u>	JM-72	AW 49579	0.2	16/04/70

<u>10a</u>	<u>mice</u>	<u>(07/08/70)</u>	<u>640 T-C 0.3</u>
<u>10b</u>	<u>mice</u>	<u>(07/08/70, 23/09/70)</u>	<u>160 T-C 0.3;</u>
	<u>chick</u>	<u>(07/08/70)</u>	<u>120 T-C 0</u>

*The structure and molecular formula are not confirmed by high resolution mass spectrometry. Many higher mass peaks are observed, the highest significant being a complex of isotopic peaks about m/e (rel intensity) 351.1483 (36, calcd for C₂₁H₂₂N₃Cl, 351.1503), with the base peak at 296.0942 (100, calcd for C₁₇H₁₅N₃Cl, 296.0955). The peak in the 280 region, at 280.0604 (6) may correspond to C₁₆H₁₁N₃Cl (calcd 280.0642).

II. Intermediates - continued

F. N-(4-Diethylamino-1-methylbutyl)-N-(2-phenylquinazolin-4-yl)acetamides



<u>11</u>	<u>R</u> ⁶	Substituent Identification	mp °	Formula Mol. Wt.	Source or Reference	
					Anal.	Calcd. % Found
<u>a</u>	H	2-phenyl*	127.5-128.5	$\text{C}_{25}\text{H}_{32}\text{N}_4\text{O}^*$ 404.54	C 74.22 H 7.97 N 13.85	KTK
<u>b</u>	C1	6-chloro-2-phenyl#	161.5-165	$\text{C}_{25}\text{H}_{31}\text{ClN}_4$ OC1# 438.99	C 68.40 H 7.12 N 12.76 C1 8.08	KTK

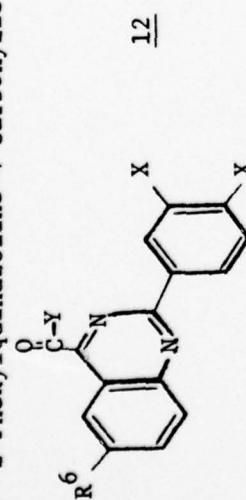
<u>11</u>	Our No.	Reed No.	Sample Size, g.	Date Received	Walter Sample Date	
<u>a</u>	JM-23	AW 49748	0.7	16/04/70	<u>11a</u>	mice (07/08/70) 640 T-C 3.9
<u>b</u>	JM-21	AW 49757	0.2	16/04/70	<u>11b</u>	mice (07/08/70, 23/09/70) 160 T-C 0.1

*This compound almost certainly does not have the structure 11a shown (on the data sheet, the 4-substituent is shown, incorrectly, as CH₃CONH-). The melting point, but not the biological test data, corresponds to that of 9b, a synthetic precursor of structure 11a. A sample, mp 244.5°, of another product from the reaction was shown by high resolution mass spectrometry to be 6b, a synthetic precursor of and also a hydrolysis product of 9b. Mass spectrum of 6b m/e (rel intensity) 222.0787 [M⁺ (60), calcd. for C₁₄H₁₈N₂O, 222.0793], 119.0375 [(M - C₇H₅N)⁺ (100), calcd for C₇H₅NO, 119.0371], 77.0350 [(M - C₈H₅N₂O)⁺ (18), calcd. for C₁₄H₁₈N₂O, 77.0391].

#The structure and molecular formula are not confirmed by high resolution mass spectrometry. There are no peaks of mass as high (438) as the proposed molecular ion. The base peak corresponds to a fragment, CH₂=N(CH₂CH₃)₂, derivable from the hypothetical sidechain; mass spectrum m/e (rel intensity) 86.0952 (100, calcd. for C₅H₁₂N, 86.0969).

G. Quinazoline-4-carboxylic Acids and Derivatives

1. 2-Phenylquinazoline-4-carboxylic Acids and Derivatives



12	X	R ⁶	Y	Substituent Identification	mp°	Formula Mol. Wt.		Anal.	Calcd. % Found	Source or Reference
						C ₁₆ H ₁₂ N ₂ O ₂ 268.30	C ₂₁ H ₁₄ N ₂ O ₂ 326.34			
a	H	H	OCH ₃	2-phenyl, methyl ester	100-112	C ₁₆ H ₁₂ N ₂ O ₂ 268.30	C 71.62	H 6.01	N 10.44	KTK
b	H	H	OC ₆ H ₅	2-phenyl, phenyl ester	130-131	C ₂₁ H ₁₄ N ₂ O ₂ 326.34	C 77.28	H 4.32	N 8.58	KTK
c	H	H	C1	2-phenyl, acid	88-91	C ₁₅ H ₉ N ₂ OCl*	C 67.04	H 3.38	N 10.43	C1 13.20
d	C1	H	ONa	2-(3,4-di- chlorophenyl), sodium salt	>370	C ₁₅ H ₇ N ₂ O ₂ NaCl ₂ 341.13	C 52.81	H 2.07	N 8.21	C1 20.79
e	C1	H	NH ₂	2-(3,4-di- chlorophenyl), amide	278-279	C ₁₅ H ₉ N ₃ OCl ₂ 318.16	C 56.62	H 2.85	N 13.21	C1 22.29
f	C1	C1	OH	6-chloro-2-(3, 4-dichloro- phenyl), acid	183	C ₁₅ H ₇ N ₂ O ₂ Cl ₃ 353.59	C 50.95	H 2.00	N 7.92	C1 30.08
g	C1	C1	OL1	6-chloro-2-(3, 4-dichloro- phenyl), lithium salt	224-226	C ₁₅ H ₆ N ₂ O ₂ LiCl ₃ 359.52	C 50.11	H 1.68	N 7.79	C1 29.59
h	C1	C1	ONa	6-chloro-2-(3, 4-dichloro- phenyl), sodium salt	155-160 dec	C ₁₅ H ₆ N ₂ O ₂ NaCl ₃ 375.58	-	-	-	KTK

*High resolution mass spectrometry on an eight-year old sample gave no peak of mass quite as high as the expected molecular ion. There was a peak at m/e 250 which may correspond to the hydrolysis product of 12c, the corresponding carboxylic acid, C₁₅H₁₀N₂O₂. The base peak corresponds to the decarboxylation product, C₁₄H₈N₂⁺; mass spectrum m/e (rel intensity) 250.0790 [M⁺(9), calcd for C₁₅H₁₀N₂O₂, 250.0742], 206.0863 [(M-CO)⁺(100), calcd for C₁₄H₈N₂⁺(38), 205.0786 [(M-CO₂)⁺(100), calcd for C₁₄H₆N₂⁺, 205.0766], 179.0733 [(M-NCCOOH)⁺(36), calcd for C₁₃H₉N, 179.0735]. The peak at m/e 205.0786 could also correspond to the loss of COCl from 12c.

II. Intermediates

G. Quinazoline-4-carboxylic Acids and Derivatives

1. 2-Phenylquinazoline-4-carboxylic Acids and Derivatives - continued

<u>12</u>	<u>X</u>	<u>R⁶</u>	<u>Y</u>	Substituent	mp°	Formula Mol. Wt.	Anal.	Calcd. % Found	Source or Reference
<u>1</u>	C1	C1	OCH ₃	6-chloro-2-(3, 4-dichloro- phenyl), methyl ester	193-193.5 192-193	C ₁₆ H ₉ N ₂ O ₂ Cl ₃ 367.62	C 52.27 H 2.47 52.21 2.34	C1 28.94 7.12 29.31	KTK
<u>1</u>	C1	C1	-O-C(=O)-NO ₂	6-chloro-2-(3,4- dichloro- phenyl), 4- nitrophenyl ester#	275-277	C ₂₁ H ₁₀ N ₃ O ₄ Cl ₃ 474.68	C 53.13 H 2.12 - -	C1 22.41 8.85 N -	KTK
<u>k</u>	C1	C1	C1	6-chloro-2-(3, 4-dichloro- phenyl), acid chloride	190-195	C ₁₅ H ₆ N ₂ OCl ₄ 372.04	C 48.42 H 1.63 - -	C1 38.12 7.53 N -	KTK
<u>1</u>	C1	C1	NH ₂	6-chloro-2-(3, 4-dichloro- phenyl), amide	303-304	C ₁₅ H ₈ N ₃ OCl ₃ 352.61	C 51.09 H 2.29 51.17 2.38	N 11.92 12.18	C1 30.16 - -
<u>m</u>	C1	C1		6-chloro-2-(3,4- dichloro- phenyl), 2- pyridyl ketone ⁺	205-230	C ₂₀ H ₁₀ N ₃ OCl ₃ 414.68	C 57.93 H 2.43 - -	N 10.13 C1 25.65 12.07 -	KTK
<u>12</u>	<u>Our No.</u>	<u>Walter Reed No.</u>	<u>Sample Size, g.</u>	<u>Date Received</u>	<u>12 Our No.</u>	<u>Walter Reed No.</u>	<u>Sample Size, g.</u>	<u>Date Received</u>	
<u>a</u>	JM-182	AW 49640	0.15	16/04/70	<u>g</u>	JM-195	AW 49631	0.3	16/04/70
<u>b</u>	JM-185 (JM-187)	AW 98518	0.2	16/04/70	<u>h</u>	JM-177 1	AW 49622 AW 49659	0.6 0.6	16/04/70 16/04/70
<u>c</u>	JM-181	AW 49711	0.3	16/04/70	<u>l</u>	JM-188	AW 49688	0.6	16/04/70
<u>d</u>	JM-168	AW 49613	0.6	16/04/70	<u>k</u>	JM-183 1	AW 49720 AW 49686	0.1 0.3	16/04/70 16/04/70
<u>e</u>	JM-166	AW 49702	0.6	16/04/70	<u>l</u>	JM-176	AW 49686	0.3	16/04/70
<u>f</u>	JM-178	AW 49604	0.3	16/04/70	<u>m</u>	JM-180	AW 49739	0.6	16/04/70

#The structure and molecular formula are not confirmed by low resolution mass spectrometry, although isotopic clusters may be consistent with the presence of chlorine. There is no molecular ion peak at 473. The highest significant mass peaks are at m/e (rel intensity) 382 (0.4) and 384 (0.4) with very few peaks having much intensity, except at 139 (5), 101 (43), 100 (16), and 87 (15), before the base peak at 86 (100).

+Footnote is on next page.

<u>12a</u>	mice	(07/08/70,	23/09/70)	160 T-C 0.1
<u>12b</u>	mice	(23/09/70)	160 T-C 0.1;	chick (10/02/71) 100 T-C 0
<u>12c</u>	mice	(07/08/70,	23/09/70)	320 T-C 0.5
<u>12d</u>	mice	(07/08/70)	640 T-C 0.7;	chick (07/08/70) 160 T-C 0
<u>12e</u>	mice	(07/08/70)	640 T-C 0.1	
<u>12f</u>	mice	(07/08/70,	23/09/70)	320 T-C 0.3; chick (07/08/70) 120 T-C 0
<u>12g</u>	mice	(07/08/70,	23/09/70)	320 T-C 0.3; chick (07/08/70) 120 T-C 0
<u>12h</u>	mice	(07/08/70)	640 T-C 2.9	
<u>12i</u>	mice	(07/08/70)	640 T-C 2.5;	chick (07/08/70) 160 T-C 0
<u>12j</u>	mice	(07/08/70)	640 T-C 0.3;	chick (07/08/70) 160 T-C 0
<u>12k</u>	mice	(07/08/70,	23/09/70)	80 T-C 0.1
<u>12l</u>	mice	(07/08/70,	23/09/70)	320 T-C 0.3; chick (07/08/70) 120 T-C 0
<u>12m</u>	mice	(07/08/70)	640 T-C 0.3	

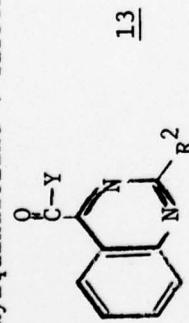
25

⁺The structure and molecular formula are not confirmed by low resolution mass spectrometry. There is no molecular ion peak at 413. The highest mass peak is at m/e (rel intensity) 391 (0.2) with very few peaks having much intensity, except at 387 (5), 385 (6), 256 (12), 160 (14), 128 (12), and 66 (9), before the base peak at 64 (100).

II. Intermediates

G. Quinazoline-4-carboxylic Acids and Derivatives - continued

2. 2-Alkylquinazoline-4-carboxylic Acids and Amides



<u>13</u>	<u>R³</u>	<u>Y</u>	<u>Substituent</u>	<u>mp°</u>	<u>Formula</u>	<u>Calcd. %</u>	<u>Source or Reference</u>
			<u>Identification</u>		<u>Mol. Wt.</u>	<u>Anal. Found</u>	
<u>a</u>	CH ₃	OH	2-methyl, acid	191-192	C ₁₀ H ₈ N ₂ O ₂	C 63.82 H 4.29 N 14.89	KTK
<u>b</u>	CH ₃	NH ₂	2-methyl, amide	172-176.5	C ₁₀ H ₉ N ₃ O	C 64.16 H 4.85 N 22.45	KTK
<u>c</u>	CF ₃	NH ₂	2-trifluoromethyl, amide *	255-263	C ₁₀ H ₆ N ₃ O ₂ F ₃ *	C 49.80 H 2.51 N 17.43	KTK

<u>13</u>	<u>Our No.</u>	<u>Walter Reed No.</u>	<u>Sample Size, g.</u>	<u>Date Received</u>
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<u>a</u>	JM-160	AW 49597	0.6	16/04/70	<u>13a</u>	mice (07/08/70) 640 T-C 0.1
<u>b</u>	JM-158	AW 49677	0.6	16/04/70	<u>13b</u>	mice (07/08/70) 640 T-C 0.1; chick (07/08/70) 120 T-C 0
<u>c</u>	JM-162	AW 49695	0.5	16/04/70	<u>13c</u>	mice (07/08/70) 640 T-C 0.1; chick (07/08/70) 120 T-C 0

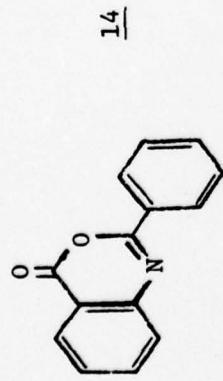
*The structure and molecular formula are not confirmed by high resolution mass spectrometry.

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II. Intermediates - continued

H. 4(4H)-3,1-Benzoxazinones

1. 2-Phenyl-4(4H)-3,1-benzoxazinone



<u>mp°</u>	<u>Formula Mol. Wt.</u>	<u>Anal.</u>	<u>Calcd. % Found</u>	<u>Source or Reference</u>	<u>Our No.</u>	<u>Walter Reed No.</u>	<u>Sample Size, g.</u>	<u>Date Received</u>
116-124	C ₁₄ H ₉ NO ₂ 223.22	C 75.32 - -	H 4.06 - -	N 6.28 - -	KTK JM-88	AW 49524 0.6	0.6	16/04/70

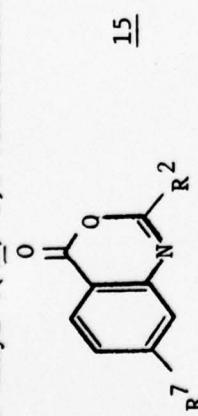
14 mice (07/08/70) 640 T-C 0.1

II. Intermediates

28

H. $4(4\text{H})$ -3,1-Benzoxazinones - continued

2. 2-Alkyl-4(4H)-3,1-benzoxazinones



<u>15</u>	<u>R²</u>	<u>R⁷</u>	<u>Substituent Identificat</u>	<u>mp°</u>	<u>Formula Mol. Wt.</u>	<u>Anal.</u>	<u>Calcd. % Found</u>	<u>Source or Reference</u>
<u>a</u>	CF ₃	H	2-trifluoromethyl*	180-181	C ₉ H ₄ NO ₂ F ₃ * 215.13	C 50.24 H 1.87 N 6.51 -	-	KTK
<u>b</u>		C1	7-chloro-2-cyclohexyl#	200-215	C ₁₄ H ₁₄ NO ₂ Cl#C 263.72	H 5.35 N 5.31 C1 13.45 -	-	KTK

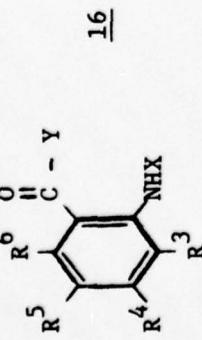
<u>15</u>	<u>Our No.</u>	<u>Walter Reed No.</u>	<u>Sample Size, g.</u>	<u>Date Received</u>
<u>a</u>	JM-144*	AW 49542	0.3	16/04/70
<u>b</u>	JM-82	AW 49533	0.6	16/04/70

*There are two compounds with our no. JM-144, 15a (AW 49542) and 17b (AW 49168), but they can be distinguished by their Walter Reed nos. This sample does not have the structure shown but is identical with compound 17b, as shown by comparison of the infrared spectra in Nujol, and by the high resolution mass spectrum m/e (rel intensity) 233.0317 [M⁺(33)], calcd for C₉H₆NO₂F₃, 233.0310, 215.0181 [(M-H₂O)⁺ or M⁺ of 15a (11)], calcd for C₉H₄NO₂F, 215.0194, 146.0172 [(M-HCF₃-OH)⁺ (146), calcd for C₈H₄NO₂, 146.0242], 90.0341 [(M-C₃H₂O₃)⁺ (44)], calcd for C₆H₄N, 90.0344].

#This sample appears to be a mixture, probably containing considerably more of the precursor 17e than of 15b, as judged from the high resolution mass spectrum m/e (rel intensity for m/e > 206 only) 283.0834 [M(37Cl)⁺ for 17e (31), calcd for C₁₄H₁₆NO₃³⁷Cl, 283.0789], 281.0816 [M⁺ for 17e (100), calcd for C₁₄H₁₆NO₃³⁵Cl, 281.0819], 263.0711 [15b (5), calcd for C₁₄H₁₄NO₂Cl, 263.0712].

II. Intermediates - continued

I. Anthranilic Acids and Derivatives



	<u>16</u>	<u>R³</u>	<u>R⁴</u>	<u>R⁵</u>	<u>R⁶</u>	<u>X</u>	<u>Y</u>	<u>Substituent</u>	<u>mp°</u>	<u>Identification</u>	<u>mp°</u>	<u>Formula *</u>	<u>Mol. Wt.</u>	<u>Anal.</u>	<u>Calcd. %</u>	<u>Found</u>	<u>Source or Reference</u>
<u>a</u>	C1	H	H	H	H	OH		3-chloro	187-192 dec			C ₇ H ₅ NOCl	154.58	C 54.39 H 3.26 N 9.06	C1 22.94	-	KTK
<u>b</u>	C1	H	H	H	H ₂ Cl	OH		3-chloro, hydrochloride	198-199.5			C ₇ H ₇ NOCl ₂	192.05	C 43.78 H 3.67 N 7.29	C1 36.93	-	KTK
<u>c</u>	H	C1	H	H	H ₂ Cl	OH		4-chloro, hydrochloride	241-242.5			C ₇ H ₇ NOCl ₂	192.05	C 43.78 H 3.67 N 7.29	C1 36.93	-	KTK
<u>d</u>	H	C1	H	H	H	OCH ₃		4-chloro, methyl ester	68-70			C ₈ H ₈ NO ₂ Cl	185.61	C 51.76 H 4.35 N 7.55	C1 19.10	-	KTK
<u>e</u>	H	H	C1	H	H	OH		5-chloro	213.5-217			C ₇ H ₅ NOCl	154.58	C 54.39 H 3.26 N 9.06	C1 22.94	-	KTK
<u>f</u>	H	H	C1	H	H	OCH ₃		5-chloro, methyl ester	63.5-65.5			C ₈ H ₈ NO ₂ Cl	185.61	C 51.76 H 4.35 N 7.55	C1 19.10	-	KTK
<u>g</u>	H	H	H	C1	H	OH		6-chloro	150-151.5			C ₇ H ₅ NOCl	154.58	C 54.39 H 3.26 N 9.06	C1 22.94	-	KTK
<u>h</u>	H	H	C1	H ₂ Cl	H	OH		6-chloro, hydrochloride	160-178 dec			C ₇ H ₇ NOCl ₂	192.05	C 43.78 H 3.67 N 7.29	C1 36.93	-	KTK

* Mass spectral data are reported on the next page.

* Mass spectral data:

16a Low resolution mass spectrum m/e (rel intensity) 173 [(M³⁷Cl)⁺ (15)], 171 [(M³⁵Cl)⁺ (47)], 155 [(M³⁷Cl - H₂O)⁺ (32)], 154 (10), 153 [(M³⁵Cl - H₂O)⁺ (100)], 127 [(M³⁷Cl - HCOOH)⁺ (10)], 126 [(M - 35Cl - COOH)⁺ (11)], 125 [(M³⁵Cl - HCOOH)⁺ (27)], 118 [(M - H₂O - Cl)⁺ (16)], 90 [(M - HCOOH - Cl)⁺ (33)].

16b Low resolution mass spectrum m/e (rel intensity) 173 [(M³⁷Cl - HCl)⁺ (16)], 171 [(M³⁵Cl - HCl)⁺ (50)], 155 [(M³⁷Cl - HCl - H₂O)⁺ (33)], 154 (10), 153 [(M³⁵Cl - HCl - H₂O)⁺ (100)], 127 [(M³⁷Cl - HCl - HCOOH)⁺ (9)], 126 [(M³⁵Cl - HCl - COOH)⁺ (9)], 125 [(M³⁵Cl - HCl - HCOOH)⁺ (23)], 118 [(M - HCl - H₂O - Cl)⁺ (14)], 90 [(M - HCl - COOH - Cl)⁺ (26)]; high resolution mass spectrum m/e (rel intensity) 173.0058 [(M - HCl)⁺ (16)], calcd for C₇H₆NO₃⁵⁷Cl, 173.0057 [(M - HCl)⁺ (48)], calcd for C₇H₆NO₃₅Cl, 171.0087 [(M - HCl - H₂O)⁺ (100)], 152.9997 [(M - HCl - H₂O)⁺ (100)], calcd for C₇H₄NO₃₅Cl, 152.9981 [(M - HCl - HC₆O₄H)⁺ (22)], calcd for C₇H₄N³⁵Cl, 125.0032], 118.0288 [(M - HC₁ - H₂O - Cl)⁺ (13)], calcd for C₇H₄NO, 118.0293], 90.0350 [(M - HCl - COOH - Cl)⁺ (20)], calcd for C₆H₄N, 90.0344].

16c Low resolution mass spectrum m/e (rel intensity) 173 [(M³⁷Cl - HCl)⁺ (18)], 171 [(M³⁵Cl - HCl)⁺ (56)], 155 [(M³⁷Cl - HCl - H₂O)⁺ (33)], 154 (13), 153 [(M³⁵Cl - HCl - H₂O)⁺ (100)], 128 [(M³⁷Cl - HCl - COOH)⁺ (16)], 126 [(M³⁵Cl - HCl - COOH)⁺ (49)], 90 [(M - HCl - COOH - Cl)⁺ (11)].

16d Low resolution mass spectrum m/e (rel intensity) 187 [(M³⁷Cl)⁺ (19)], 185 [(M³⁵Cl)⁺ (58)], 156 [(M³⁷Cl - CH₃O)⁺ (12)], 155 [(M³⁷Cl - CH₃OH)⁺ (35)], 154 [(M³⁵Cl - CH₃O)⁺ (100)], 128 [(M³⁷Cl - COOCH₃)⁺ (14)], 126 ³[(M³⁵Cl - COOCH₃)⁺ (44)], 99 ³[(M³⁵Cl - COOCH₃)⁺ (13)], 90 [(M³⁵Cl - HCOOCH₃ - Cl)⁺ (90)]; high resolution mass spectrum m/e (rel intensity) 187.0214 [M⁺ (18)], calcd for C₈H₈N₂O³⁷Cl, 187.0214 [M⁺ (54)], calcd for C₈H₈NO₃₅Cl, 185.0243], 156.0035 [(M - CH₃O)⁺ (11), calcd for C₇H₈NO₃₇Cl, 156.0030], 154.9979 [(M - CH₃O)⁺ (40), calcd for C₇H₈NO₃₅Cl, 154.9952], 154.0069 [(M - CH₃O)⁺ (38)], calcd for C₇H₅NO₃₅Cl, 154.0060], 153.0002 [(M - CH₃O)⁺ (106), calcd for C₇H₅NO₃₅Cl, 152.9981] 127.9923 [(M - COOCH₃)⁺ (14)], calcd for C₇H₅N³⁷Cl, 128.0488], 123.9860 [(M - COOCH₃)⁺ (27)], calcd for C₆H₅N³⁵Cl, 126.0111], 39.0004 [(M - COOCH₃ - HCN)⁺ (11), calcd for C₅H₄N³⁵Cl, 99.0001], 90.0317 [(M - HCOOCH₃ - Cl)⁺ (12), calcd for C₆H₄N, 90.0344].

16e Low resolution mass spectrum m/e (rel intensity) 173 [(M³⁷Cl)⁺ (16)], 171 [(M³⁵Cl)⁺ (52)], 155 [(M³⁷Cl - H₂O)⁺ (32)], 153 [(M³⁵Cl - H₂O)⁺ (100)], 127 [(M³⁷Cl - HCOOH)⁺ (12)], 126 [(M³⁵Cl - COOH)⁺ (23)], 90 [(M - HCOOH - Cl)⁺ (28)].

16f The low resolution mass spectrum suggests that the sample at time of analysis (8 1/2 years later) was quite impure; m/e (rel intensity) 185 [M⁺ (100)].

16g Low resolution mass spectrum m/e (rel intensity) 173 ³[(M³⁷Cl)⁺ (17)], 171 [(M³⁵Cl)⁺ (52)], 155 [(M³⁷Cl - H₂O)⁺ (33)], 154 (11), 153 [(M³⁵Cl - H₂O)⁺ (100)], 128 [(M³⁷Cl - COOH)⁺ (15)], 126 [(M³⁵Cl - COOH)⁺ (47)], 90 [(M - HCl - HCOOH - Cl)⁺ (17)].

16h Low resolution mass spectrum m/e (rel intensity) 173 [(M³⁷Cl - HCl)⁺ (14)], 171 [(M³⁵Cl - HCl)⁺ (44)], 155 [(M³⁷Cl - HCl - H₂O)⁺ (32)], 154 (10), 153 [(M³⁵Cl - HCl - H₂O)⁺ (100)], 128 [(M³⁷Cl - HCl - COOH)⁺ (24)], 90 [(M - HCl - HCOOH - Cl)⁺ (24)].

II. Intermediates - continued

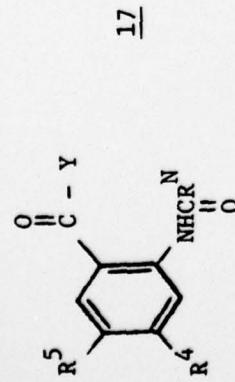
I. Anthranilic Acids and Derivatives

<u>16</u>	<u>Our No.</u>	<u>Walter Reed No.</u>	<u>Sample Size, g.</u>	<u>Date Received</u>
<u>a</u>	JM-119	AW 98527	0.6	16/04/70
<u>b</u>	JM-95	AW 49195	0.2	16/04/70
<u>c</u>	JM-109	AW 49211	0.1	16/04/70
<u>d</u>	JM-77	AW 49239	0.6	16/04/70
<u>e</u>	JM-55B	AW 49202	0.6	16/04/70
<u>f</u>	JM-50	AW 49220	0.6	16/04/70
<u>g</u>	JM-122	AW 49177	0.6	16/04/70
<u>h</u>	JM-108	AW 49186	0.7	16/04/70

16a mice (23/09/70) 640 T-C 0.3; chick (10/02/71) 160 T-C 016b mice (23/09/70) 320 T-C 0.716c mice (23/09/70) 80 T-C 3.116d mice (07/08/70) 640 T-C 0.516e mice (07/08/70) 640 T-C 0.1; chick (07/08/70) 160 T-C 016f mice (07/08/70) 640 T-C 0.1; chick (07/08/70) 160 T-C 016g mice (07/08/70) 640 T-C 2.3; chick (07/08/70) 160 T-C 016h mice (07/08/70) 640 T-C 0.1; chick (07/08/70) 160 T-C 0

II. Intermediates - continued

J. N-Acylanthranilic Acids and Derivatives



17

17	Substituent				mp°	Formula Mol. Wt.	Anal.	Calcd. % Found	Source or Reference			
	R ^N	R ⁴	R ⁵	Y								
a CH ₃	H	H	OH	N-acetyl	191-192.5	C ₉ H ₉ NO ₃	C 60.33 H 5.06	N 7.82	KTK			
b CF ₃	H	H	OH	N-trifluoroacetyl	188-190	C ₉ H ₆ NO ₃ F ₃	C 46.36 H 2.59	N 6.01	KTK			
c	H	H	OH	N-cyclohexane-carbonyl *	178-180 231-232	C ₁₄ H ₁₇ NO ₃ *	C 46.48 45.87	H 2.67 2.60	5.94 5.92	KTK		
d		H	OH	N-(4-nitrobenzoyl)*	272-275	C ₁₄ H ₁₀ N ₂ O ₅ *	C 58.74 68.41	H 3.52 6.01	N 9.79 7.42	KTK		
e		C1	H	OH	4-chloro-N-cyclohexanecarbonyl	233-234.5	C ₁₄ H ₁₆ NO ₃ C1	C 59.68 59.48	H 5.72 5.56	N 4.97 4.92	C1 12.59 12.76	KTK
f		C1	H	OCH ₃	4-chloro-N-cyclohexanecarbonyl, methyl ester	135.5-136	C ₁₅ H ₁₈ NO ₃ C1	C 60.91 60.93	H 6.13 6.11	N 4.74 4.62	C1 11.99 12.09	KTK
g		H	C1	OCH ₃	5-chloro-N-cyclohexanecarbonyl, methyl ester	143.5-144	C ₁₅ H ₁₈ NO ₃ C1	C 60.91 61.20	H 6.13 6.11	N 4.74 4.64	C1 11.99 12.08	KTK
h		H	C1	OH	5-chloro-N-(4-nitrobenzoyl)	291-293	C ₁₄ H ₉ N ₂ O ₅ C1*	C 52.43 52.86	H 2.83 3.73	N 8.74 9.88	C1 11.05 13.04	KTK
i		H	C1	OCH ₃	5-chloro-N-(4-nitrobenzoyl), methyl ester	264-267	C ₁₅ H ₁₁ N ₂ O ₅ C1*	C 53.82 52.35	H 3.31 2.98	N 8.37 8.28	C1 10.59 12.70	KTK
j		H	C1	NH ₂	5-chloro-N-(4-nitrobenzoyl), amide*	294-302 268.5-270	C ₁₄ H ₁₀ N ₃ O ₄ C1*	C 52.59 51.42	H 3.15 3.21	N 13.15 9.32*	C1 11.09 10.12	KTK
k		H	NO ₂	OH*#	5-nitro-N-(4-nitrobenzoyl)*#	270-284.5	C ₁₄ H ₉ N ₃ O ₇	C 50.76 -	H 2.74 -	N 12.69 -	KTK	

(footnotes are on next page)

17c After 8 2/3 years, the sample appeared to have partially decomposed, as indicated by the appearance of brown specks. From the high resolution mass spectrum, the compound appears to be a mixture with a significant peak at 265 but not corresponding to $C_4H_{19}NO_4$ (the salt of anthranilic acid and cyclohexane-carboxylic acid), no molecular ion peak at 247 corresponding to 17c but a significant peak at 230 corresponding to loss of hydroxyl from 17c, a base peak at 137 corresponding to the molecular ion of anthranilic acid (also a possible fragmentation product of 17c), and a significant peak at 120 corresponding to the loss of hydroxyl from anthranilic acid (or of cyclohexanecarboxylate from $\frac{1}{2}17c$; m/e 265.0632 (33), 230.1192 [(M - OH)⁺ (52), calcd for $C_4H_{14}NO_2$, 230.1181], 137.0515 [(M - $C_6H_4CO + H$)⁺ (100), calcd for $C_7H_7NO_2$, 137.0477], 120.0446 [(M - $C_6H_{11}O$)⁺ (57), calcd for C_7H_6NO , 120.0449].

17d The structure and molecular formula are not confirmed by low resolution mass spectrometry. The sample appears to contain a mixture of 4-nitrobenzoic acid (the base peak at 167 corresponds to the molecular ion) and anthranilic acid (a major peak at 137 corresponds to the molecular ion), or a salt of the two. Major peaks occur at m/e (rel intensity) 167 (100, $O_2NC_6H_4COOH^+?$), 137 (26, $H_2NC_6H_4COOH^+?$), 121 (43, $C_6H_4COOH^+?$), 109 (17), 73 (78, $C_6H^+?$), 65 (51), 44 (27, CO_2^+).

17h Low resolution mass spectrum m/e (rel intensity) 304 [(M^{37Cl - H₂O⁺)⁺ (6)], 302 [(M^{35Cl - H₂O⁺)⁺ (17)], 272 (10), 187 (12), 185 (29), 173 [(C₆H₅NO₂)^{37Cl⁺)⁺ (16)], 171 [(C₆H₅NO₂)^{35Cl⁺)⁺ (30)], 156 (19), 155 [(C₆H₅NO₂)^{37Cl⁺)⁺ (38)], 154 (63), 153 [(C₆H₅NO₂)^{35Cl⁺)⁺ (100)], 150 (17), 128 [(C₆H₅NO₂)^{37Cl⁺)⁺ (19)], 127 [(C₆H₅NO₂)^{37Cl⁺)⁺ (22)], 126 [(C₆H₅NO₂)^{35Cl⁺)⁺ (51)], 125 [(C₆H₄NO₂)^{35Cl⁺)⁺ (36)], 120 [(C₆H₄NO₂)^{37Cl⁺)⁺ (77)], 98 (25), 92 (19), 81 (10), 90 [(C₆H₄N)⁺ (38)], 89 (33); high resolution mass spectrum m/e (rel intensity) 304.0030 [(M - H₂O⁺)⁺ (15), calcd for $C_6H_5NO^{37Cl}$], 302.0058 [(M - H₂O⁺)⁺ (55), calcd for $C_6H_5NO^{35Cl}$], 302.0094 [(15), calcd for $C_6H_5NO^{37Cl}$], 173.0057 [171.0087], 154.9842 [(45), calcd for $C_6H_4NO^{37Cl}$, 154.9952], 153.9896 [(12), calcd for $C_6H_5NO^{35Cl}$, 154.0060], 152.9830 [(100), calcd for $C_6H_4NO^{35Cl}$, 152.9981]; on another spectrum: 305.0103 [(M - OH)⁺ (12), calcd for $C_14H_8N^{204^{37Cl}}$, 305.0143], 303.0155 [(M - OH)⁺ (9), calcd for $C_14H_8N^{204^{35Cl}}$, 303.0172], 302.0124 [(M - H₂O⁺)⁺ (24), calcd for $C_14H_7N^{204^{35Cl}}$, 302.0094], 173.0052 [(30), calcd for $C_7H_6NO^{2^{37Cl}}$, 173.0057], 171.0109 [(67), calcd for $C_7H_6NO^{2^{35Cl}}$, 171.0087], 152.9975 [(100), calcd for $C_7H_4NO^{35Cl}$, 152.9981], 125.0037 [(54), calcd for $C_6H_4N^{35Cl}$, 125.0032], 120.0461 [(70), calcd for C_7H_6NO , 120.0449], 120.0210 [(11), calcd for $C_7H_4O_2$, 120.0211].}}}}}}}}}}}

(footnotes continued on next page)

* Mass spectral data:

171 Low resolution mass spectrum m/e (rel intensity) 336 [(M³⁷Cl)⁺ (2)], 334 [(M³⁵Cl)⁺ (8)], 322 [(M³⁷Cl - CH₂)⁺ (5)], 320 [(M³⁵Cl - CH₂)⁺ (15)], 304 [(M³⁷Cl - CH₃OH)⁺ (6)], 302 [(M³⁵Cl - CH₃OH)⁺ (18)], 155 [(C₇H₄NO³⁷Cl)⁺ (9)], 153 [(C₇H₄NO³⁵Cl)⁺ (29)], 151 [(C₇H₅NO?)⁺ (8)], 150 [(C₇H₄NO₃)⁺ (100)], 120 [(C₇H₆NO)⁺ or (C₇H₄O₂)⁺ (31)], 104 [(C₇H₄O)⁺ (52)], 92 [(C₆H₄O?)⁺ (25)]; high resolution mass spectrum m/e (rel intensity) 334.0377 [M⁺ (8), calcd for C₁₅H₁₁N₂O₅Cl, 320.0200]; on another spectrum: 334.0207 [M⁺ (8), calcd for C₁₅H₁₁N₂O₅Cl, 334.0357], 322.0209 [(M - CH₂)⁺ (16), calcd for C₁₄H₉N₂O₅Cl, 322.0170], 320.0201 [(M - CH₂)⁺ (69), calcd. for C₁₄H₉N₂O₅Cl, 320.0200].

171 Consistent with the low nitrogen analysis, the low resolution mass spectrum of another sample shows that the sample consists principally of a mixture of the methyl ester starting material (171, 334) and the acid hydrolysis product (17h, 320) and fragmentation products derivable therefrom: m/e (rel intensity) 334 (7, C₁₅H₁₁N₂O₅Cl, 171?), 320 (18, C₁₄H₉N₂O₅Cl, 17h?), 302 (12, C₁₄H₇N₂O₄Cl, 17h - H₂O or 171 - CH₃OH, similar to 15?), 153 (34, C₇H₂NOCl?), 150 (100, O₂NC₆H₄CO?), 120 (39, C₇H₄O?)⁺, 104 (51, C₆H₄CO?).

17k Low resolution mass spectrum m/e (rel intensity) 376 (0.8), 331 (M⁺ 0.1), 286 [(M - COOH)⁺ (19)], 269 [(M - H₂CO₃)⁺ (20)], 268 [(M - COOH - H₂O)⁺ (100)], 224 [(M - CO₂ - HNO₃)⁺ (49)], 178 [(M - CO₂ - HNO₃ - NO₂)⁺ (22)], 167 [C₇H₅NO₄⁺, 58], 150 [C₇H₄NO₃⁺, 68], 146 (50), 121 (39), 120 (26), 119 (43), 104 (66), 92 (33), 90 (39).

Incorrectly given as the methyl ester in the name and structure on the data sheet for this compound.

II. Intermediates - continued

J. N-AcyLanthranilic Acids and Derivatives

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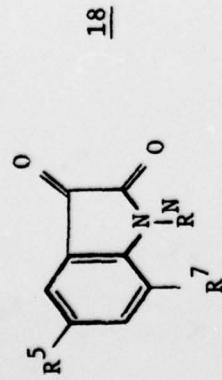
<u>17</u>	<u>Our No.</u>	<u>Walter Reed No.</u>	<u>Sample Size, g.</u>	<u>Date Received</u>
<u>a</u>	JM-149	AW 47646	0.6	16/04/70
<u>b</u>	JM-144*	AW 49168	0.4	16/04/70
<u>c</u>	JM-151	AW 98509	0.6	16/04/70
	(JM-58C)			
<u>d</u>	JM-37	AW 98536	0.4	16/04/70
	(JM-36-E)			
<u>e</u>	JM-98	AW 49284	0.7	16/04/70
<u>f</u>	JM-79	AW 49293	0.6	16/04/70
<u>g</u>	JM-52	AW 49275	0.6	16/04/70
<u>h</u>	JM-35	AW 49257	0.4	16/04/70
<u>i</u>	JM-41F	AW 49926	0.6	23/04/70
	(JM-41)			
<u>j</u>	JM-39	AW 49266	0.6	16/04/70
<u>k</u>	JM-43	AW 49300	0.6	16/04/70

*There are two samples with our no. JM-144, 15a (AW 49542) and 17b (AW 49168), but they can be distinguished by their Walter Reed nos.

<u>17a</u>	mice (07/08/70) 640 T-C 0.3; chick (07/08/70) 160 T-C 0	<u>171</u>	mice (07/08/70) 640 T-C 1.1; chick (07/08/70) 160 T-C 0
<u>17b</u>	mice (07/08/70), 23/09/70) 640 T-C 0.3		
<u>17c</u>	mice (23/09/70) 640 T-C 0.3; chick (10/02/71) 160 T-C 0	<u>171</u>	mice (07/08/70) 640 T-C 0.5; chick (07/08/70) 160 T-C 0
<u>17d</u>	mice (23/09/70) 640 T-C 0.1; chick (10/02/71) 120 T-C 0	<u>17k</u>	mice (07/08/70) 640 T-C 0.5; chick (07/08/70) 160 T-C 0
<u>17e</u>	mice (07/08/70) 640 T-C 0.3		
<u>17f</u>	mice (07/08/70) 640 T-C 0.5; chick (07/08/70) 160 T-C 0		
<u>17g</u>	mice (07/08/70) 640 T-C 0.9		
<u>17h</u>	mice (17/02/72) 320 T-C 0.3		

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K. Isatins and Derivatives



<u>18</u>	R ⁵	R ⁷	R ^N	Substituent Identification		mp°	Formula Mol. Wt.	Anal.	Calcd. % Found	Source or Reference
				Identification	mp°					
a	H	H	COCH ₃	N-acetyl	146-147.5	C ₁₀ H ₇ NO ₃ 189.16	C 63.49 H 3.73 N 7.41 - - -	-	-	KTK
b	H	H	COCF ₃	N-trifluoroacetyl	163-166	C ₁₀ H ₄ NO ₃ F ₃ * 243.14	C 49.40 H 1.66 N 5.76 - - -	-	-	KTK
c	H	H	CO-C ₆ H ₃ (Cl) ₂ -C ₆ H ₃ (Cl) ₂	N-(3,4-dichloro-benzoyl)	228-230	C ₁₅ H ₇ NO ₃ Cl ₂ 320.13	C 56.28 H 2.20 N 4.38 55.99 2.12	C1 22.15 4.34 21.87	-	KTK
d	C1	H	Na	5-chloro, sodium salt	-	C ₈ H ₃ NO ₂ NaCl ₂ 203.57	C 47.20 H 1.48 N 6.88 - -	C1 17.42 - -	-	KTK
e	C1	H	CO-C ₆ H ₃ (Cl) ₂ -C ₆ H ₃ (Cl) ₂	5-chloro-N-(3,4-di-chlorobenzoyl)	199-200	C ₁₅ H ₆ NO ₃ Cl ₃ 354.58	C 50.81 H 1.70 N 3.95 50.58 1.82	C1 30.00 3.84 29.76	-	KTK
f	C1	C1	Na	5,7-dichloro, sodium salt	-	C ₈ H ₂ NO ₂ NaCl ₂ 238.02	C 40.37 H 0.85 N 5.89 - -	C1 29.79 - -	-	KTK
g	C1	C1	CO-C ₆ H ₃ (Cl) ₂ -C ₆ H ₃ (Cl) ₂	5,7-dichloro-N-(3,4-dichlorobenzoyl)	156-158	C ₁₅ H ₅ NO ₃ Cl ₄ 389.03	C 46.31 H 1.29 N 3.60 - -	C1 36.46 - -	-	KTK

* After being kept for 8 1/2 years, the sample of 18b was observed to evolve a gas which fumed in air (trifluoroacetic acid) and to contain a mixture of the original yellow crystals as well as orange crystals (isatin) resulting from partial hydrolysis by atmospheric moisture. The sample was redried under vacuum at room temperature; low resolution mass spectrum m/e (rel intensity) 244 [(M + 1)+ 1.5], 243 (M+, 9), 215 [(M - CO)+ (50)], 147 [(C₈H₅NO₂, isatin)+ (16)], 146 [(C₈H₄NO₂, M - COCF₃)+ (100)], 119 [(C₇H₅NO, isatin - CO)+ (15)], 118 [(C₇H₄NO, M - COCF₃ - CO)+ (8)], 92 [(C₆H₆N)+ (10)], 91 [(C₆H₅N)+ (8)], 90 [(C₆H₄N, M - COCF₃ - 2CO)+ (62)], high resolution mass spectrum m/e (rel intensity) 243.0156 [M+ (8), calcd for C₁₀H₄NO₃F₃, 243.0143], 215.0200 [(M - CO)+ (38), calcd for C₉H₄NO₂F₃, 215.0194], 147.0305 [(isatin)+ (12), calcd for C₈H₅NO₂, 147.0320], 146.0278 [(M - COCF₃)+ (100), calcd for C₈H₄NO₂, 146.0242], 90.0361 [(M - COCF₃ - 2CO)+ (71), calcd for C₆H₄N, 90.0344]; on another spectrum: 244.0112 [(M + H)+ (5), calcd for C₁₀H₅NO₃F₃, 244.0222], 243.0149 [M+ (6), calcd for C₁₀H₄NO₃F₃, 243.0143], 215.0147 [(M - CO)+ (41), calcd for C₉H₄NO₂F₃, 215.0194], 146.0246 [(M - COCF₃)+ (100), calcd for C₈H₄NO₂, 146.0242], 119.0388 [(isatin - CO)+ (85), calcd for C₇H₅NO, 119.0371], 118.0252 [(M - COCF₃ - CO)+ (11), calcd for C₇H₄NO, 118.0293], 90.0369 [(M - COCF₃ - 2CO)+ (46), calcd for C₆H₄N, 90.0344].

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II. Intermediates - continued

K. Isatins and Derivatives

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<u>18 Our No.</u>	<u>Walter Reed No.</u>	<u>Sample Size, g.</u>	<u>Date Received</u>
<u>a</u>	JM-153	AW 49328	0.5 16/04/70
<u>b</u>	JM-156	AW 49319	0.6 16/04/70
<u>c</u>	JM-165	AW 49337	0.2 16/04/70
<u>d</u>	JM-175	AW 49346	0.6 16/04/70
<u>e</u>	JM-170	AW 49355	0.6 16/04/70
<u>f</u>	JM-167	AW 49364	0.6 16/04/70
<u>g</u>	JM-173	AW 49373	0.6 16/04/70
<u>18a</u>	mice (07/08/70)	640 T-C 0.1	
<u>18b</u>	mice (07/08/70)	640 T-C 0.1; chick (07/08/70) 160 T-C 0.1	
<u>18c</u>	mice (07/08/70, 23/09/70) 100 T-C 0	160 T-C 3.1 and 2.9, 320 5 toxic deaths at 4 days; chick (07/08/70)	
<u>18d</u>	mice (07/08/70)	640 T-C 0.3	
<u>18e</u>	mice (07/08/70)	640 T-C 0.1; chick (07/08/70) 160 T-C 0	
<u>18f</u>	mice (07/08/70)	640 T-C 0.1; chick (07/08/70) 160 T-C 0	
<u>18g</u>	mice (07/08/70)	640 T-C 0.1	

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II. Intermediates - continued

I. Miscellaneous

1. 1-Cinnamylpyridinium Chloride



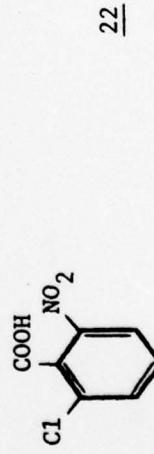
2. Trifluoroacetamide



3. 3,4-Dichlorobenzoic Anhydride



4. 6-Chloro-2-nitrobenzoic Acid



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II. Intermediates - continued

39.

L. Miscellaneous

<u>mp°</u>	<u>Mol. Wt.</u>	<u>Formula</u>	<u>Anal.</u>	<u>Calcd. % Found</u>	<u>Source or References</u>	<u>Our No.</u>	<u>Walter Reed No.</u>	<u>Sample Size, g.</u>	<u>Date Received</u>
<u>19</u>	<u>33-35</u>	<u>$C_{14}H_{14}NCl$</u>	<u>$C\ 72.56\ H\ 6.09\ N\ 6.05$</u>	<u>C1 15.30</u>	<u>DT</u>	<u>D1</u>	<u>AE 72407</u>	<u>0.5</u>	<u>18/07/68</u>
		<u>231.72</u>	<u>-</u>	<u>-</u>					
<u>20</u>	<u>128-129.5</u>	<u>$C_2H_2NOF_3^*$</u>	<u>$C\ 21.25\ H\ 1.78\ N\ 12.39$</u>	<u>C1 -</u>	<u>KTK</u>	<u>JM-140</u>	<u>AW 47628</u>	<u>0.6</u>	<u>16/04/70</u>
		<u>113.04</u>	<u>-</u>	<u>-</u>					
<u>21</u>	<u>157-158</u>	<u>$C_{14}H_6O_3Cl_4$</u>	<u>$C\ 46.19\ H\ 1.66\ N\ -$</u>	<u>C1 38.96</u>	<u>KTK</u>	<u>JM-300</u>	<u>AW 47637</u>	<u>0.5</u>	<u>16/04/70</u>
		<u>364.02</u>	<u>$45.86\ 1.72$</u>	<u>-</u>					
<u>22</u>	<u>159-160</u>	<u>$C_7H_4NO_4Cl$</u>	<u>$C\ 41.71\ H\ 2.00\ N\ 6.95$</u>	<u>C1 17.59</u>	<u>KTK^r</u>	<u>JM-99</u>	<u>AW 49248</u>	<u>0.6</u>	<u>16/04/70</u>
		<u>201.57</u>	<u>-</u>	<u>-</u>					

19 mice (01/10/68) 80 T-C 0.2, 160 T-C 1.3 but 3 toxic deaths at 4 days, 320 and 640 5 toxic deaths at 3 days; chick (19/11/68) 60 T-C 0.6, 120 T-C 0.8 but 1 toxic death at 1 day, 240 5 toxic deaths at 1 day (06/03/71) 320 5 toxic deaths at 1 day; P. gall. A. aegypti (06/11/68) 0.1% 20% toxic deaths (control 0%) neg.

20 mice (07/08/70) 640 T-C 0.3

21 mice (07/08/70) 640 T-C 0.3

22 mice (07/08/70) 640 T-C 1.3; chick (07/08/70) 160 T-C 0

* Low resolution mass spectrum of 20 m/e (rel intensity) 115 [(CF₃COOH)⁺ (0.2)], 114 [(CF₃COOH)⁺ (1.3)], 97 [(CF₃CO)⁺ (8)], 95 [(CF₃CN or CF₂COOH)⁺ (6)], 86 [(CF₃OH)⁺ (1.0)], 69 [(CF₃)⁺ (100)], 51 [(CHF₂)⁺ (40)], 50 [(CF₂)⁺ (15)], 45 [(COOH)⁺ (94)], 44 [(CONH₂)⁺ (10)]; high resolution mass spectrum m/e (rel intensity) 115.0009 [(M + 2)⁺ (0.5), calcd for CF₃COOH, 115.006], 113.9938 [(M + 1)⁺ (1.2), calcd for CF₃COOH, 113.9928], 96.9896 [(M - NH₂)⁺ (6), calcd for CF₃CO, 96.9900], 94.9937 [(M - H₂O)⁺ (3.5), calcd for CF₃CN, 94.9983, calcd for CF₂COOH, 94.9944], 85.9972 [(M - CO)⁺ (2.3), calcd for CF₃OH, 85.9979], 68.9910 [(M - CONH₂)⁺ (100), calcd for CF₃, 68.9952].

39

Sources

MAS = M. Akram Sandhu, postdoctoral research, 1967-69.

KTK = Kung Tu Kuo, postdoctoral research, 1967-69.

TRA = Terence R. Ashe, undergraduate research assistant, 1967-68.

JOB = Jerold O. Bahls, graduate research assistant, U.S. Public Health Service Grant No. 5 R01 CA04073-09,10 "The Reactions of Indoles with Unsaturated Compounds", March 22- December 31, 1967.

SYA = Sarvottam Y. Ambekar, postdoctoral research, 1968-69.

JBH = Joseph B. Hanson, NSF Undergraduate Research Participant, summers of 1965 and 1967.

DT = Dennis Toskas, NSF Undergraduate Academic Year Research Participant and senior thesis research, 1968.

40

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- (k) Joseph B. Hanson (with W. E. Noland), National Science Foundation Undergraduate Research Participant, Univ. of Minn.; (a) Summer 1965; (b) Summer 1967.
- (l) (a) T. A. K. Smith and H. Stephen, Tetrahedron, 1, 38-44 (1957); (b) H. Stephen and G. Wadge, J. Chem. Soc., 4420-4421 (1956); (c) V. S. Patel and S. R. Patel, J. Indian Chem. Soc., 42, 531-535 (1965); (d) J. L. Rodgers and J. P. Milionis (to American Cyanamid Co.), U.S. Patent 3,169,129, Feb. 9, 1965; Chem. Abstr., 62, 14696a (1965) (the compounds are not listed in the abstract).
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- (o) Mark A. Jaglowski (with W. E. Noland), National Science Foundation Undergraduate Research Participant, University of Minn., Summer 1962.

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Personnel Receiving Contract Support

(including graduate degree received, if any)

In chronological order of employment:

- (1) Dr. Kung Tu Kuo, postdoctoral Research Specialist, June 23, 1967-Aug. 31, 1969, full time.
- (2) Robert J. Strange, Graduate Research Assistant, Aug. 16-Sept. 15, 1967, half time.
- (3) Dennis P. Landucci, Graduate Research Assistant, Sept. 1-15, 1967, half time. M.S. thesis Sept. 1969, on an unrelated subject: "A Study of the Bromination of Methylindoles and a Related Oxidation Product from 2,3-Dimethylindole".
- (4) Terrence R. Ashe, Undergraduate Research Assistant, Sept. 1, 1967-Oct. 31, 1968, part time.
- (5) Dr. M. Akram Sandhu, postdoctoral Research Specialist, Oct. 18, 1967-Nov. 15, 1969, full time.
- (6) Dr. Sarvottam Y. Ambekar, postdoctoral Research Specialist, Feb. 1, 1968-Aug. 31, 1969, full time.

Related Work Not Supported by the Contract

- (1) Joseph B. Hanson, NSF Undergraduate Research Participant, summer 1967, "Synthesis and Reactions of Ten Quinazolinones and Their Precursors".
- (2) Jerald K. Rasmussen, NSF Undergraduate Research Participant and senior thesis student, academic year 1967-68, "Synthesis and Ring Expansion of 2-(2-Pyridyl)isatogens".
- (3) Dennis Toskas, NSF Undergraduate Academic Year Research Participant and senior thesis student, winter and spring 1968, "Carbon and Nitrogen Ring Insertion Reactions of 2-Styrylisatogen".
- (4) Tetsuo Kakehi, M.S. thesis, Sept. 1969, "Ring Expansion Reactions of Biisatogens".
- (5) Lily C. Tomlin, M.S. thesis, April 1971, "Variation of Reagents in the Nitrogen Ring Expansion Reaction of 2-Phenylisatogen".
- (6) R. James Puhl, Ph.D. thesis, May 1971, "Reactions of Isatogen Analogs"; Diss. Abstr. Int. B, 32, 4498-4499 (1972).
- (7) Jerold O. Bahls, Ph.D. thesis, Aug. 1972, "Substituent Effects in Ring Expansion Reactions of Isatogens with Acetylenes"; Diss. Abstr. Int. B, 33, 5723-5724 (1973).